RESPONSE

I. Status of the Claims

The Summary page and page 2 of the Third Action include certain errors, in that the Summary page lists claim 16 as both withdrawn and rejected, and does not account for claim 14, and that the Action at page 2, second paragraph omits claim 43 from the claims under consideration.

An amendment was submitted after the Third Action, which was denied entry. Accordingly, prior to the present communication, claims 1-30 and 34-43 were pending. Presently, claims 1, 12, 20-23, 30 and 39-42 have been amended to focus on the elected species and to even further improve the clarity of the invention. Claims 15-19 have been canceled without prejudice as drawn to non-elected species. Claims 44-48 have been added, which are fully supported by the application as filed and are unified with the examined claims.

Claims 1-14, 20-30 and 34-48 are therefore in the case. According to the revisions to 37 C.F.R. § 1.121(c), a copy of the pending claims is provided in the amendment section.

II. Entry of Amendments

The present amendments are entitled to entry as a matter of right in light of the concurrent Request for Continued Examination (RCE).

III. Support for the Claims

Support for the amended claims and new claims is to be found throughout the original application as filed. In light of the claims canceled to date, no fees should be due for entry of the new claims, however, any small entity fees deemed necessary should be deducted from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4001.002282.

Claim 1 has been revised to remove the detectably-labeled antibody of the non-elected species and to thereby focus on the second anti-cancer agent of the elected species.

Claim 12 has been revised to even further clarify that where the kits comprise first and second anti-aminophospholipid antibodies, or antigen-binding fragments thereof, the first antibody binds to a first aminophospholipid and the second antibody binds to another aminophospholipid. The revisions clarify the original claim language and also better accord with claim 13. The change is supported by claims 12 and 13, and throughout the specification, *e.g.*, at least at page 7, lines 1-2.

Each of claims 20-23 has been revised to depend from claim 1 instead of claim 19, which has been cancelled as redundant in light of the revisions to claim 1.

Claim 30 has been revised to specify that the claimed kit "further" comprises a detectably-labeled anti-aminophospholipid antibody, but only in addition to the second anti-cancer agent of the elected species.

Each of claims 39-42 has also been revised to remove the detectably-labeled antibody of the non-elected species and to focus on the second anti-cancer agent of the elected species, as in claim 1.

New claim 44 is based upon claim 34 and further defines certain preferred examples of the second anti-cancer agents. The functional definition of the unconjugated antibody, or antigen-binding fragment thereof, as binding to an aminophospholipid on the luminal surface of the vascular endothelial cells of the blood vessels of a vascularized tumor is supported by claims 39-42 and throughout the specification, *e.g.* at least at page 9, lines 2-3. Preferred second anti-cancer agents, other than the unconjugated anti-aminophospholipid antibody or antigen-binding fragment thereof, are recited as: (i) an agent that increases aminophospholipid

expression, or injures or induces apoptosis in the tumor blood vessel endothelium, as supported by the specification at least at least at page 33, lines 5-12; and (ii) an agent that kills tumor cells or anti-angiogenic agent that inhibits metastasis of tumor cells, as supported by the specification at least from page 32, line 27 to page 33, line 3.

Dependent claim 45 separately recites a second anti-cancer agent as in claim 44 (b)(i), which increases aminophospholipid expression, or injures or induces apoptosis in the tumor blood vessel endothelium, supported by the specification at least at page 33, lines 5-12.

Claim 46 exemplifies agents in accordance with claim 45 as taxol, vincristine, vinblastine, neomycin, a combretastatin, a podophyllotoxin, TNF-α, angiostatin, endostatin, vasculostatin, an $\alpha_v\beta_3$ antagonist, a calcium ionophore or as a calcium-flux inducing agent (specification at page 33, lines 5-12), H_2O_2 or thrombin (Example XIV), an inflammatory cytokine (page 40, line 18; page 121, lines 16-23; Example XIV) or interleukin-4 (page 40, line 18; page 121, line 18).

Dependent claim 47 separately recites a second anti-cancer agent as in claim 44 (b)(ii), which kills tumor cells or is an anti-angiogenic agent that inhibits metastasis of tumor cells, as supported by the specification at least from page 32, line 27 to page 33, line 3.

Claim 48 exemplifies agents in accordance with claim 47 as an anti-tumor cell immunoconjugate, a chemotherapeutic agent or an anti-angiogenic agent, which are supported throughout the specification, with particular written description support at least from page 33, line 13 to page 35, line 21.

It will therefore be understood that no new matter is included within the amended or new claims.

IV. Restriction and Species Issues

The Action states that claims 2, 13, 15-18, 30 and 36-38 "are withdrawn from further consideration, as being drawn to nonelected species. Applicant timely traversed the restriction (election) requirement in Paper No. 14" (Fourth Action at page 2). These statements are in error.

First, the original species elections were made without traverse.

Second, the continued withdrawal of many of the claims directed to the originally non-elected species is improper and inconsistent with the claims already examined on the merits. For example, claim 13 should be examined with claim 3, claims 30 and 38 should be examined with claim 1, and claim 37 should be examined with claims 1 and 34.

In the interest of progressing the application to allowance as quickly as possible, Applicants presently elect to cancel claims directed to non-elected species. Accordingly, claims 15-19 have been canceled without prejudice as drawn to the non-elected species of detectably-labeled antibodies.

V. Withdrawal of the Rejection Under 35 U.S.C. § 102(e)

Claims 1, 3-12, 14, 19-22 and 39-43 in the present application stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,300,308 to Schroit ("Schroit"). Although Applicants respond in full below, the Office has already re-assessed Schroit in a co-pending application and withdrawn a § 102(e) rejection based on the same reasoning that was set forth in this Action. Accordingly, the rejection is improper and should be withdrawn.

In co-pending application Serial No. 09/351,149 ("the '149 application"), the Office mailed a Fourth and Non-Final Official Action ("the Fourth Action") on October 22, 2002. The Fourth Action in the '149 application also included a § 102(e) rejection over Schroit, the

reasoning of which was the same as that set forth in the present application (compare the respective Actions at pages 2-4, where the text is almost exactly the same).

Applicants submitted a response in both applications on April 22, 2003, addressing the § 102(e) rejections in substantially the same manner. As the Fourth Action in the '149 application was non-final, Applicants' response was considered on the merits, whereupon the § 102(e) rejection over Schroit was withdrawn (Fifth Action mailed July 15, 2003 in the '149 application, see Fifth Action throughout, bottom of page 2, and page 3, third paragraph).

The reasoning of the Office concerning Schroit of record in the present application, which dates back to October 22, 2002, is thus no longer current and has been replaced by the reasoning of July, 2003, which not only re-assessed Schroit, but withdrew the § 102(e) rejection based thereon. Accordingly, the present rejection is unfounded and should be withdrawn.

VI. Rejection of Claims 1, 3-12, 14, 19-22 and 39-43 Under 35 U.S.C. § 102(e)

Claims 1, 3-12, 14, 19-22 and 39-43 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Schroit. Although Applicants respectfully traverse, the Action's concerns are overcome.

A. The Office has Re-assessed Schroit and Withdrawn the § 102(e) Rejection

As set forth above (**Section V**), the Office has reconsidered Schroit and withdrawn a § 102(e) rejection based on the same reasoning as advanced in the present case. The following detailed response (**Section VI,B**) is substantially the same as the response that the Office found to be effective to overcome the rejection. The present rejection is therefore unfounded and should be withdrawn.

B. Response on the Merits

The following response should not be interpreted as an acquiescence that a proper *prima facie* rejection was established, nor that the effective filing of date Schroit is earlier than the effective filing date of the present application, nor as waiving any rights to establish a date of invention earlier than the effective filing date of Schroit.

Within examined claims 1, 3-12, 14, 19-29, 34, 35 and 39-43, each of claims 23-29, 34 and 35 are free from this ground of rejection. Without acquiescing with the rejection in any way, Applicants presently introduce claims 44-48, which are based upon and extend claims 34 and 35. As agreed by the Office in the '149 application, and as further detailed below, claims 1, 3-12, 14, 19-29, 34, 35 and 39-43, and new claims 44-48, are novel over Schroit.

Claim 1 recites a kit comprising a first anti-cancer agent in the form of a first antibody, or an antigen-binding fragment thereof, which binds to an aminophospholipid; and a second anti-cancer agent other than the first anti-aminophospholipid antibody or fragment thereof.

Schroit does not teach or suggest a kit comprising a first anti-cancer agent in the form of a first antibody, or an antigen-binding fragment thereof, which binds to an aminophospholipid, in combination with a second anti-cancer agent other than the first anti-aminophospholipid antibody or fragment thereof.

The rejection is largely based on the position that the first and second anti-cancer agents recited in present claim 1 can be exactly the same agent and, consequently, that the kits of claim 1 would be anticipated by a kit containing two aliquots of the same first anti-aminophospholipid antibody or fragment thereof. Such a position is in error and has subsequently been reconsidered and withdrawn by the Office (**Sections V and VI,A**). In particular, the Office now assesses Schroit as failing to disclose "the use of other suitable

antiphospholipid antibodies in combination with a second anticancer agent" (Fifth Action in the '149 application at page 3).

Despite the plain meaning of the claim, which recites that the second anti-cancer agent is an anti-cancer agent other than the first anti-aminophospholipid antibody or fragment thereof, the Action takes the position that the claim "is not limited to two distinct antibodies directed to aminophospholipids" and that the second anti-cancer agent "encompasses any anticancer agent" (Third Action at page 3). According to the broadest reasonable interpretation of the claims, the second anti-cancer agent encompasses any second anti-cancer agent other than an anti-aminophospholipid antibody or fragment thereof. To determine otherwise would be inconsistent with the language of the claim itself and the controlling case law, which requires that the broadest reasonable interpretation of the claims must be consistent with the interpretation that those skilled in the art would reach. *In re Cortright,* 49 USPQ2d 1464, 1468 (Fed. Cir. 1999).

The Action's claim interpretation, which ignores the claim term "other than", attempts to read a limitation out of the claims, which is prohibited. Every element of a claim has meaning; the language of the claim as a whole must be considered and an interpretation should not be reached that renders a clause superfluous. *Genentech Inc. v. Chiron Corp.*, 42 USPQ2d 1608, 1612 (Fed. Cir. 1997). Claims should not be read so as to improperly broaden the scope of the claims 'reading out' the limitations in claim language. *Lockheed Martin Corp. vs. Space Systems/Loral Inc.* 58 USPQ2d 1671, 1678 (Fed. Cir. 2001).

There is no reasonable interpretation of claim 1 to support the Action's contention that this claim is not limited to two distinct anti-cancer agents. The § 102(e) rejection, essentially based on the position that the first and second anti-cancer agents recited in claim 1 can be the same, is therefore in error and must be withdrawn, as occurred in the '149 application. Should

the Office maintain the interpretation of the claims from October 22, 2002, and the resultant § 102(e) rejection, Applicants respectfully request that the Office identify the particular statutory or judicial authority and scientific reasoning underlying the proposed claim interpretation and, further, explain why a different conclusion was reached in the '149 application.

Aside from the improper claim interpretation, which underlies most of the rejection, the Action's additional comments also fail to support the § 102 rejection. A rejection on the grounds of anticipation requires the disclosure, in a single reference, of every element of a claimed invention and requires that each and every facet of the claimed invention be identified in the applied reference. *Minnesota Mining & Mfg. v. Johnson & Johnson Orthopaedics, Inc.*, 24 USPQ2d 1321 (Fed. Cir. 1992). The Action's reference to different biological components mentioned in isolation in different sections of Schroit is insufficient to support an anticipation rejection of the present claims, which are drawn to "a kit", *i.e.*, a combination of components that are designed for use together:

> "The kits of the present invention will also typically include a means for containing the vials, or such like, and other component, in close confinement for commercial sale, such as, *e.g.*, injection or blow-molded plastic containers into which the desired vials and other apparatus are placed and retained."
>
> Specification at page 105, lines 15-18.

The lines and phrases in Schroit quoted at pages 3 and 4 of the Action do not teach or suggest kits with the elements of the present claims.

Schroit from column 7, line 67 to column 8, line 1 concerns one container with a PS composition and another container including "a matrix, solution, or other suitable delivery device" for applying "the composition" to the body. That is, one PS composition and one delivery device. The Action states that Schroit refers to PS compositions, and thus contends that

Schroit discloses kits that can contain "a second anti-aminophospholipid antibody conjugate" (Fourth Action at page 3).

In response, the claims at issue are not directed to an "anti-aminophospholipid antibody conjugate", but to a naked or unconjugated anti-aminophospholipid antibody or fragment thereof in combination with a second, distinct anti-cancer agent. Even if Schroit refers to "PS compositions", including anti-PS antibody compositions, this would not anticipate the claimed invention. It is important to note that Schroit concerns only PS. Therefore, *even if* Schroit refers to "PS compositions", including anti-PS antibody compositions, such compositions *would have to be the same*. There is no teaching or suggestion in Schroit of a kit comprising a first anti-cancer agent in the form of an anti-aminophospholipid antibody, or fragment thereof, and a second anti-cancer agent other than the first anti-aminophospholipid antibody or fragment, as in the claimed invention.

The Action's further comments regarding claim 21, PS-polypeptide conjugates, separate moieties to be conjugated and diphtheria toxoid (Fourth Action at pages 3 and 4) have largely been taken out of context of the Schroit document (see below), but in any event, these separate aspects of Schroit do not teach or suggest the kits of the claimed invention.

Schroit at claim 21 does not recite an "antibody-therapeutic construct" (Third Action at page 3). Claim 21 of Schroit concerns a method for generating a lipid-specific antibody response by administering a PS-polypeptide conjugate in which PS is conjugated to the carrier BSA, KLH, BGG, diphtheria toxin or β2-glycoprotein I. The administered composition is thus not an antibody-therapeutic agent construct. In any event, the claims at issue are not directed to an antibody-therapeutic agent construct, but to a naked or unconjugated anti-aminophospholipid antibody or fragment thereof and a second, distinct anti-cancer agent.

Schroit's reference to an antibody that can exist in "separate moieties to be conjugated by user of the kit" (Third Action at page 3) concerns immunodetection reagents alone, in particular, "antibody-label conjugates", which can be in fully conjugated form or as intermediates or separate moieties to be conjugated (Schroit at column 6, lines 50-51).

The discussion of diphtheria toxoid in Schroit is limited to its use as a carrier, *i.e.*, when conjugated to PS. There is no teaching regarding the use of diphtheria toxoid as any form of therapeutic agent alone.

Importantly, irrespective of the context of the PS-polypeptide conjugates, immunodetection moieties to be conjugated and diphtheria toxoid carriers in Schroit, the Action has still not identified any aspect of Schroit that teaches or suggests a kit comprising an anti-aminophospholipid antibody or fragment thereof in combination with a second, distinct anti-cancer agent.

For at least the foregoing reasons, claims 1, 3-12, 14, 19-22 and 39-43 are therefore novel over Schroit. Claims 13, 30 and 38, which have been improperly withdrawn from consideration, are also novel over Schroit.

As claims 34 and 35 are free from the § 102(e) rejection, each of claims 44-48, which are based upon claims 34 and 35, are also novel over Schroit. Each of claims 44-48, directed to the therapeutic kits of claim 34 in conjunction with defined properties of the first antibody, and particularly, with additional features of the second anti-cancer agent, is also novel over Schroit for the same and additional reasons.

Claim 44 is directed to a therapeutic kit in accordance with claim 34 in which the second anti-cancer agent is defined according to certain preferred features, particularly as an anti-cancer agent that (i) increases aminophospholipid expression, or injures or induces apoptosis in the

tumor blood vessel endothelium; or that (ii) kills tumor cells or is an anti-angiogenic agent that inhibits metastasis of tumor cells. Claims 45 and 46 separately recite the two groups of second anti-cancer agents, and claims 47 and 48 provide particular examples of each. Claims 44-48 are therefore novel for the same reasons as claim 34, and further because Schroit does not teach or suggest anti-cancer agents that increase aminophospholipid expression, injure or induce apoptosis in tumor blood vessel endothelium, or that kill or inhibit the metastasis of tumor cells, let alone teach or suggest such anti-cancer agents as part of a kit in accordance with the present claims.

The § 102(e) rejection over Schroit is therefore overcome and should be withdrawn.

VII. Withdrawal of Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3-12, 14, 19-29, 34, 35 and 39-43 in the present application stand rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over Schroit in view of U.S. Patent No. 5,632,991 to Gimbrone ("Gimbrone") and Umeda *et al.*, *J. Immunol.*, 143:2273-2279, 1989, ("Umeda"). Although Applicants respond in full below, the Office has already re-assessed Schroit and Gimbrone in a co-pending application and withdrawn a § 103(a) rejection based on reasoning analogous to that set forth in this Action. Accordingly, the rejection is improper and should be withdrawn.

In the '149 application, the Fourth Action also included a § 103(a) rejection over Schroit and Gimbrone in combination with a third reference. In the '149 application, the third reference was Blackenberg, whereas the third reference in the present rejection is Umeda. Despite the different third reference, the reasoning of the § 103(a) rejection in the '149 application was analogous to the § 103(a) rejection in the present application (compare the respective Actions at pages 4-5, where the text is essentially the same).

Applicants submitted a response in both applications on April 22, 2003, addressing the § 103(a) rejections in substantially the same manner. In the '149 application, Applicants' response was considered on the merits, whereupon the § 103(a) rejection over Schroit, Gimbrone and a third reference was withdrawn (Fifth Action in the '149 application, see Fifth Action throughout and bottom of page 2).

The reasoning of the Office concerning Schroit of record in the present application, which dates back to October 22, 2002, is no longer current and has been replaced by the reasoning of July, 2003, which not only re-assessed Schroit, but withdrew a § 103(a) rejection based on Schroit, Gimbrone and a third reference. This is strong evidence that the present rejection is unfounded and should be withdrawn.

VIII. Rejection of Claims 1, 3-12, 14, 19-29, 34, 35 and 39-43 Under 35 U.S.C. § 103(a)

The Action rejects claims 1, 3-12, 14, 19-29, 34, 35 and 39-43 under 35 U.S.C. § 103(a) as allegedly being legally obvious over Schroit in view of Gimbrone and Umeda. Although Applicants respectfully traverse, the Action's concerns are addressed.

A. The Office has Re-assessed Schroit and Withdrawn a § 103(a) Rejection

As set forth above (**Section VII**), the Office has reconsidered Schroit and withdrawn a § 103(a) rejection based on reasoning analogous to that advanced in the present case. The following detailed response (**Section VIII,B**) is analogous to the response that the Office found effective to re-assess Schroit and withdraw a § 103(a) rejection based upon Schroit, Gimbrone and a third reference. The present rejection is similarly overcome and should be withdrawn.

B. Response on the Merits

The Action again takes the position that "the instant second anticancer agent encompasses any anticancer agent" (Third Action at page 4). The claims clearly recite a first

anti-cancer agent in the form of a first antibody, or an antigen-binding fragment thereof, which binds to an aminophospholipid and a second anti-cancer agent other than the first anti-aminophospholipid antibody or fragment thereof. Therefore, in the broadest reasonable interpretation of the claims, the second anti-cancer agent encompasses any second anti-cancer agent other than an anti-aminophospholipid antibody or fragment thereof.

Any other interpretation of the claims would be inconsistent with the plain language of the claim itself and the controlling case law. *In re Cortright, supra; Lockheed Martin Corp. vs. Space Systems/Loral Inc., supra.* Should the Office maintain its interpretation of the claims contrary to their plain meaning, Applicants respectfully request that the Office identify the particular authority underlying the proposed claim interpretation and, further, explain why a different conclusion was reached in the '149 application.

The § 103(a) rejection, like the § 102(e) rejection, is essentially based on the erroneous claim interpretation and the position that the first and second anti-cancer agents recited in the claims can be the same. As the interpretation of the claims set forth in the Action is clearly in error, the § 103(a) rejection is based on faulty reasoning and is *prima facie* improper and should be withdrawn. Indeed, the analogous rejection in the '149 application was withdrawn, with the Action agreeing that Schroit fails to disclose "the use of other suitable antiphospholipid antibodies in combination with a second anticancer agent" (Fifth Action in the '149 application at page 3). The present rejection is further overcome for the following additional reasons.

The Action contests Applicants' last response on the basis that one cannot show non-obviousness by attacking references individually where the rejections are based upon a combination of references (Third Action at page 4). In fact, the scope and content of the prior art must be ascertained before the obviousness or nonobviousness of the claimed subject matter can

be determined. *Graham v. John Deere Co.*, 148 USPQ 459, 467 (U.S.S.Ct. 1966). Moreover, although the Action refers to the combination of references after formulating the rejection, some suggestion to combine the disclosure of two or more references in an attempt to establish *prima facie* obviousness must be established before the P.T.O. may combine references. *In re Fine*, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). The Action's assessment of the references is anyway incorrect and does not actually support their combination.

After setting forth the rejection, the Action takes the position that the three cited references are viewed to be in the same field of endeavor and are considered combinable because "each reference is directed to specific receptor molecule on the surface of human vascular endothelial cells associated with vascularized tumor" (Third Action at page 5). This statement not only improperly characterizes the references, but is derived from the present application and not from the cited art, and therefore has no place in an obviousness enquiry. It is impermissible to use the claims as a frame and the prior-art references as a mosaic to piece together a facsimile of the claimed invention. *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 USPQ2d 1434 (Fed. Cir. 1988).

Schroit concerns PS and reports that, as opposed to the situation in normal cells, PS may appear at the surface of tumor cells (Schroit throughout, *e.g.*, column 16, lines 27-33). Gimbrone concerns E-selectin expression on activated endothelium in certain diseases or infections, particularly in inflammation, and in connection with the metastatic spread of tumor cells (Gimbrone throughout, *e.g.*, Abstract, column 4, line 57 to column 5, line 7). Umeda concerns the direct immunization of PS-coated *Salmonella* into mouse spleen and stereo-specific aspects of antigen recognition by monoclonal antibodies (Umeda throughout, *e.g.*, Abstract and page 2274).

None of Schroit, Gimbrone or Umeda teaches or suggests expression of PS, other aminophospholipids, E-selectin or any other specific receptor molecule on the surface of human vascular endothelial cells associated with a vascularized tumor. The statement in the Action at page 5 is therefore in error and the first ground advanced to support the combination of references is without merit. By referring to information from the present application, rather than from any of the cited references, this statement also evidences the Action's improper use of hindsight in formulating the rejection. To imbue one of ordinary skill in the art with knowledge of the invention in suit, where no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher. *W.L. Gore Assoc., Inc. v. Garlock, Inc.*, 220 USPQ 303, 312-313 (Fed. Cir. 1983).

The Action at page 5 further takes the position that Schroit, Gimbrone and Umeda are combinable because they are "used for the same purpose". This statement is also in error and thus fails to support the proposed combination or the resultant § 103 rejection. The purpose of Schroit is immunization with PS-polypeptide conjugates to generate PS-specific antibodies, which may bind to tumor cells; the purpose of Gimbrone is treat diseases and infections associated with E-selection expression on activated endothelium, particularly inflammation; and the purpose of Umeda is direct intrasplenic immunization with PS-coated *Salmonella* and stereo-specific analysis of PS recognition by antibodies. These three references are therefore not directed to the same purpose and the references have been improperly combined.

Importantly, even if combined, Schroit, Gimbrone and Umeda do not teach or suggest the presently claimed invention, and particularly do not teach or suggest a kit comprising a first

antibody, or an antigen-binding fragment thereof, which binds to an aminophospholipid and a second anti-cancer agent other than such a first anti-aminophospholipid antibody or fragment.

In attempting to show a suggestion towards the claimed kits in Schroit, the Action refers to Schroit at column 7, line 67 to column 8, line 1 and states, "Schroit sets forth that multiple PS antibody compositions can be used in Schroit's kit. Therefore, Schroit's suggests [*sic*] kits that can contain containers with a second anti-aminophospholipid antibody conjugate" (Third Action at page 4). As set forth above, the claims at issue are not directed to first or second "anti-aminophospholipid antibody conjugates", but to a naked or unconjugated anti-aminophospholipid antibody or fragment thereof in combination with a second, distinct anti-cancer agent.

Even if Schroit refers to "multiple PS antibody compositions", including multiple anti-PS antibody compositions, there is no suggestion of a kit in accordance with the claimed invention. It is important to note that Schroit concerns only PS. Therefore, *even if* Schroit refers to multiple anti-PS antibody compositions, any such compositions *have to be the same*. Schroit therefore cannot suggest a kit comprising a first anti-cancer agent in the form of an anti-aminophospholipid antibody, or fragment thereof, and a second anti-cancer agent other than the first anti-aminophospholipid antibody or fragment, as in the claimed invention. The Office now appears to agree (see Fifth Action in the '149 application, particularly page 3).

The present Action next takes the position that "the instant therapeutic constructs within the kits do not exclude such constructs [PS-polypeptide conjugates] as taught by Schroit" (Third Action bridging pages 4 and 5). Should the Action be referring to the first anti-cancer agent, the anti-aminophospholipid antibody or fragment of the claims clearly excludes PS-polypeptide conjugates as in Schroit. Should the Action be implying that a PS-polypeptide conjugate as in

Schroit could be a second anti-cancer agent within the scope of the claims, this is far removed from rendering the invention of claims 1, 3-12, 14, 19-29, 34, 35 and 39-43 legally obvious.

It is well established under the law that an invention must be viewed in its entirety in formulating an obviousness rejection. The test for obviousness is not whether individual differences between the claims and the prior art are obvious but, rather, whether the claimed invention as a whole is obvious. *In re Buehler*, 185 USPQ 781 (CCPA 1975). "The entirety of a claimed invention, including the combination viewed as a whole, the elements thereof, and the properties and purposes of the invention must be considered." *In re Wright*, 6 USPQ 2d 1959 (Fed. Cir. 1988).

The Action has still not identified any aspect of Schroit that teaches or suggests a kit comprising a first antibody or fragment thereof that binds to an aminophospholipid in combination with a second, distinct anti-cancer agent. The line of argument that a PS-polypeptide conjugate of Schroit would be a second anti-cancer agent within the scope of the claims pertains to only one element of the claimed kit, and lacks any suggestion of the claimed invention *as a whole*.

Schroit therefore fails to teach or suggest the claimed invention. Indeed, the acknowledged novelty of several claims, such as claims 34 and 35, and the lack of a § 103 rejection of any claim based upon Schroit *alone* is an admission that Schroit does *not suggest* the presently claimed invention. The Action therefore relies on Gimbrone and Umeda to cure the deficiencies of Schroit (Third Action at page 5). However, Gimbrone and Umeda have been improperly combined with Schroit, and even if properly combined, Schroit, Gimbrone and Umeda together fail to teach or suggest the kits of the present invention.

Neither Gimbrone nor Umeda teach or suggest the claimed kits or second anti-cancer agents, or in any way cure the deficiencies of Schroit. Gimbrone is silent as to antibodies that bind to aminophospholipids (Second Action at page 8). Umeda concerns intrasplenic immunization methods to generate anti-phospholipid antibodies, but only for use in investigating molecular mechanisms of PS interactions (Umeda at page 2273, column 2, second paragraph). The Office agrees that "Umeda does not teach the use of his antibodies in kits for diagnostic or therapeutic purposes" (Second Action at page 9). Thus, the secondary references each fail to teach or suggest the first anti-cancer agent of the claimed kits.

The Action cites Gimbrone and Umeda to "supplement the teachings of Schroit to further provide for a second anticancer agent or therapeutic agent" (Third Action at page 5). It appears that Gimbrone, as well as Umeda, in fact lacks any teaching or suggestion of a kit with first and second therapeutic agents of any type. Gimbrone and Umeda particularly fail to teach or suggest a kit with a first and second anti-cancer agent. Gimbrone was earlier cited as concerning second E-selectin-based therapeutic agents at columns 12, 14 and 15 (Third Action at page 8), but these sections of Gimbrone are limited to an anti-E-selectin antibody, fragment or conjugate when used alone. The Office admitted that Umeda does not teach the use of a therapeutic agent (Second Action at page 9). The secondary references thus fail to teach or suggest kits with two distinct anti-cancer agents, as required by the present claims.

In failing to teach or suggest both the first and second anti-cancer agents required by the present claims, Gimbrone and Umeda are incapable of curing the admitted deficiencies of Schroit. For at least the foregoing reasons, claims 1, 3-12, 14, 19-29, 34, 35 and 39-43 are therefore novel and non-obvious over Schroit, Gimbrone and Umeda, even if properly combined.

Certain of the pending claims are also patentable over the cited references for various additional reasons[1].

Claims 39-42 recite kits in which the anti-aminophospholipid antibodies or fragments are functionally defined as binding to an aminophospholipid on the luminal surface of tumor vascular endothelial cells and as exerting particular anti-vascular effects. These claims are further patentable as the cited references do not teach or suggest the expression of aminophospholipids on the luminal surface of tumor blood vessels or anti-vascular effects of anti-aminophospholipid antibodies, let alone teach or suggest a kit comprising such antibodies in combination with a second anti-cancer agent.

The surprising discovery that aminophospholipids are accessible, stable markers of tumor vasculature (specification at page 4, lines 29-30), as recited in claims 39-42, also underlies many surprising features of claims 1, 19-29, 34, 35 and 44-48. This finding in itself was particularly surprising, as the tumor vascular endothelial cells are normal cells, taught in the prior art to preserve PS in the inner leaflet (see Schroit at column 16, lines 28-31). Relatively stable PS expression at the cell surface of normal cells was not known prior to the present invention.

The finding that PS was a marker of the normal cells of the tumor vasculature provided a means for effective therapy, overcoming the problems associated with tumor cell targeting, such as tumor cell resistance, antigen escape and effective penetration into the tumor. The inventors also unexpectedly discovered that naked antibodies against aminophospholipids are capable of specifically localizing to tumor vasculature and inducing tumor blood vessel destruction and

---

[1]Claims drawn to kits in which the first anti-cancer agent is an antibody or fragment that binds to phosphatidylethanolamine, although withdrawn from consideration, are further patentable, as the cited references do not teach or suggest a therapeutic antibody that binds to phosphatidylethanolamine, let alone such an antibody as part of a kit in combination with a second, distinct anti-cancer agent. Schroit teaches away from these aspects of the invention by the objective to produce highly-specific anti-PS antibodies (Schroit at column 2, line 36) and by the

tumor necrosis *in vivo* in the absence of conjugation to effector molecules. The invention thus provides single component therapeutics directed against tumor vasculature for use in the safe and effective treatment of solid tumors (specification at page 5, lines 5-10).

Importantly, the translocation of aminophospholipids to the surface of tumor vascular endothelial cells was further discovered to occur, at least in a significant part, independently of cell damage and apoptopic or other cell-death mechanisms (specification at page 5, lines 12-14). This discovery of sufficiently stable expression on morphologically intact tumor-associated vascular endothelial cells, which is again in contrast to the prior art (as evidenced by Schroit), was an important step in the development of effective therapies (specification at page 5, lines 15-18).

In addition to providing effective anti-vascular tumor therapy with naked antibodies, as opposed to the difficulties associated with tumor cell targeting, the present discovery of sufficiently stable aminophospholipid expression on normal tumor vasculature endothelial cells gave rise to the combined anti-cancer therapeutics described in the present application and recited in the pending claims. In particular, a first antibody or fragment that binds to an aminophospholipid on the luminal surface of the vascular endothelial cells of the blood vessels of a vascularized tumor and another agent selected for "simultaneously or sequentially administering to the animal a therapeutically effective amount of at least a second anti-cancer agent" (specification from page 32, line 11 to page 33, line 12; see also **Section J** of the specification). Therefore, the present invention, unlike the cited prior art, provides for the intelligent selection of first and second anti-cancer agents in a kit for use together.

---

description of the resultant antibodies as being able to recognize PS but not DPOE (dioleoyl phosphatidylethanolamine) in a bilayer membrane (Schroit at column 25, lines 24-26).

These aspects of the invention are highlighted in claims 44-48, which are directed to therapeutic kits in which the second anti-cancer agent is selected for combined use according to the guidance provided in the specification. A second anti-cancer agent administered at a biologically effective time *prior* to the anti-aminophospholipid antibody is taught to (i) increase aminophospholipid expression, or injure or induce apoptosis in the tumor blood vessel endothelium (specification at page 33, lines 5-12); whereas a second anti-cancer agent administered at a biologically effective time *subsequent* to the anti-aminophospholipid antibody is taught to (ii) kill tumor cells or to be an anti-angiogenic agent that inhibits metastasis of tumor cells (specification from page 32, line 27 to page 33, line 3).

Schroit, Gimbrone and Umeda, even if properly combined, do not teach or suggest anti-cancer agents that increase aminophospholipid expression, injure or induce apoptosis in tumor blood vessel endothelium, or that kill or inhibit the metastasis of tumor cells, let alone teach or suggest such agents as the second anti-cancer agent in a kit comprising a first anti-cancer agent in the form of an unconjugated antibody or fragment thereof that binds to an aminophospholipid on the luminal surface of the vascular endothelial cells of the blood vessels of a vascularized tumor. The present application, in contrast, teaches the rationale for selecting such agents in combination along with detailed teaching concerning second anti-cancer agents within each category.

The manuscript enclosed as **Exhibit A** to Applicants' last response provides actual data to support the reasoning in the application, showing that various factors and tumor-associated conditions known to be present in the tumor microenvironment are able to cause PS translocation

in cultured endothelial cells[2]. Hypoxia/reoxygenation, acidity, thrombin, and inflammatory cytokines, such as IL-1α, IL-1β, TNFα and IFN, are all shown to induce PS exposure without causing cytotoxicity. Hydrogen peroxide is also shown to be a strong inducer of PS, and inflammatory cytokines and hypoxia-reoxygenation are shown to have greater than additive effects, supporting the inventors' surprising findings that factors in tumors interact to give amplified effects on PS-exposure on the normal tumor vascular endothelial cells *in vivo*. All such information, and its effective use to provide the kits of the claimed invention, exists in the present application but not in the cited art.

The rejection under 35 U.S.C. § 103(a) is thus overcome and should be withdrawn.

IX. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance and such favorable action is respectfully requested. Should Examiner Sharareh have any questions or comments, or identify any informalities, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,
Williams, Morgan & Amerson, P.C.
Customer No. 23720

Shelley P.M. Fussey, Ph.D.
Reg. No. 39,458
Agent for Applicant

[2]It is not believed to be necessary to forward an additional copy of this Exhibit, which is present in the Office's file for the present application.

10333 Richmond, Suite 1100
Houston, Texas, 77042
(713) 934-4079
Date: November 21, 2003